TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR DURART 600 (DANURAVIR ETHANOLATE EQUIVALENT TO DARUNAVIR 600 MG) FILM COATED TABLETS

Version number 0.1

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1. Introduction

Durart 600 (Darunavir Ethanolate) is a generic medicine of innovator product PREZISTA 600 mg film-coated tablets by Janssen-Cilag, International NV. Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. It belongs to ATC code J05AE10 - Antivirals for systemic use, protease inhibitors. Durart is approved in Tanzania for use in adults and children.

1.1 Product details

Registration number	TAN 21 HM 0063
Brand name	Durart 600
Generic name, strength and form	Each Film coated Tablet contains: Darunavir Ethanolate equivalent to Darunavir 600 mg
ATC classification	J05AE10 - Antivirals for systemic use, protease inhibitors
Distribution category	POM
Country of origin	India
Associated product	Durart 800 film coated tablets registered with registration number TAN 21 HM 0064
Marketing Authorization Holder	Mylan Laboratories Limited, Plot No. 564/A/22, Road No. 92, Jubilee Hills, Hyderabad - 500034, Telangana, India. Email: kulbhushan.ganotra@mylan.in
Local Technical Representative	Pyramid Pharma Limited, 1st floor, TTCL Building, Garden Road/ New Bagamoyo Road, Kijitonyama, P. O. Box 16215, **Dar Es Salaam.** Email: aokoe@pyramidpharma.com

1.2 Assessment procedure

The application for registration of Durart 600 was submitted on 02 December, 2016. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 24 December, 2020.

1.3 Information for users

Visual description of the finished product	White to off-white, film coated, oval, biconvex tablet debossed with 'M' on one side of the tablet and "DE6" on other side
Primary packing material	Round, blue opaque HDPE bottle fitted with blue opaque HDPE cap closure with desiccator sachet. Pack size: 60 film coated tablets
Secondary packing materials	A printed carton box which includes one HDPE bottle of 60 tablets along with package insert
Shelf-life and storage condition	24 Months. Do not store above 30°C
Route of administration	Oral

Therapeutic indications	Darunavir, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection. Darunavir, co-administered with cobicistat is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in adult patients Darunavir 600 mg tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 3 years and at least 40 kg body weight who are: - antiretroviral therapy (ART)-naïve - ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l. In deciding to initiate treatment with Darunavir in such ART-experienced patients, genotypic testing should guide the use of Darunavir

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC.

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: Durart 600

Composition: Each film-coated tablet contains: Darunavir Ethanolate equivalent to Darunavir 600 mg

Pack size: 60 tablets in Blue HDPE bottle

Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Do not store above 30^0C. Store in the original container

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Referred to IFU.

The details of the primary pack include:
Brand name and strength: Durart 600 (Darunavir 600 mg)

Manufacturing details: batch number, manufacturing date, expiry date are indicated

Name of manufacturer: Mylan Laboratories Limited

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of DMF.

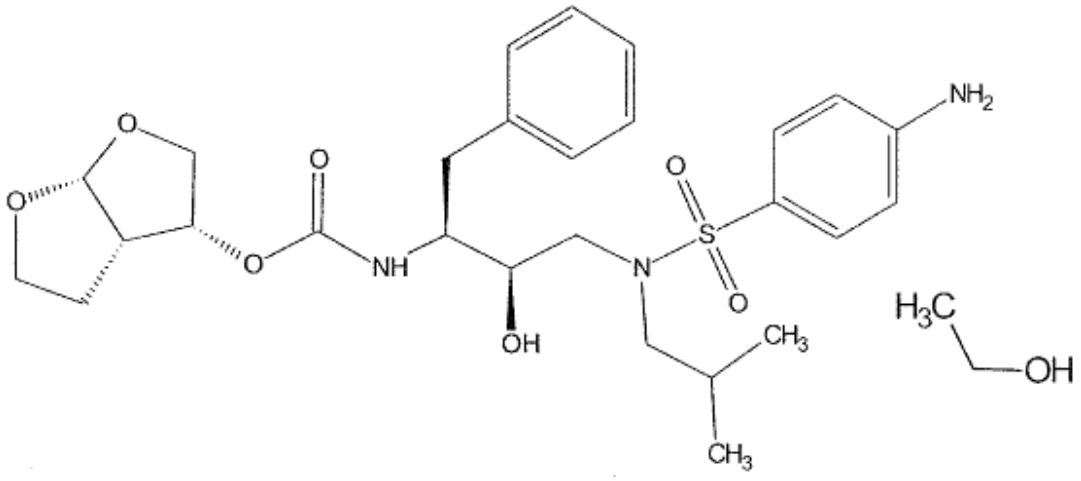
General Information

Darunavir Ethanolate API is non-compendia.

Molecular formula: $C_{40}H_{50}N_8O_6.2HCl$

Chemical name: [(1S, 2R)-3-[[(4-amino phenyl) sulfonyl] (2-methyl propyl) amino]-2-hydroxy-1-(phenyl methyl) propyl] carbamic acid (3R, 3aS, 6aR)-hexahydrofuro[2,3-b]-furan-3-yl ester ethanol corresponding to the molecular formula $C_{27}H_{37}N_3O_7S.C_2H_6O$

Structure:



General properties

Darunavir is a white to light brown colour slightly hygroscopic powder, slightly soluble in aqueous solutions, freely soluble in acetone, sparklingly soluble in ethyl acetate. Darunavir Ethanolate has five chiral centers. The active substance manufacturer commercially produces [(1S, 2R)-3-[[(4-amino phenyl) sulfonyl] (2-methyl propyl) amino]-2-hydroxy-1-(phenyl methyl) propyl] carbamic acid (3R, 3aS, 6aR)-hexahydrofuro[2,3-b]-furan-3-yl ester ethanol. Control of isomer has been included in the drug substance specification.

Darunavir exhibits polymorphism. The active substance manufacturer is consistently manufacturing crystalline form. Crystalline form control has been included in the active substance specification.

Critical physico-chemical properties of the API were solubility, particle size distribution, and polymorphism.

Manufacture

Darunavir API manufacturer is Mylan Laboratories Limited (Unit 1), Survey No. 10/42, Gaddapotharam, Kazipally Industrial Area, Medak District – 502319, Telangana, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration Government of Telangana, India. Darunavir API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The Darunavir is non compendia, specifications were set as per in-house standards and ICH guidelines. The parameters monitored during quality control are: description, solubility, identification (by IR and HPLC), water content (by KF), residue on ignition, heavy metals, related substances (HPLC), assay (HPLC), Isomer-1 (HPLC), Content of Ethyl alcohol (GC), residual solvents (GC), Identification of Polymorph (PXRD) and Particle size (Malvern). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system
The re-test period of Darunavir API is 60 months when packed in translucent LDPE bag and stored at or below 25^0C.

Quality of the Finished Pharmaceutical Product

Formulation

Durart 600 is a white to off-white, film coated, oval, biconvex tablet debossed with 'M' on one side of the tablet and "DE6" on other side. Such 60 film coated tablets are packed in a round, blue opaque HDPE bottle fitted with blue opaque HDPE cap closure with desiccator sachet. The HDPE bottle is secondarily packed in a printed carton box along with package insert.

Durart 600 contains the API Darunavir Ethanolate and other ingredients listed here after: Hypromellose (15 mPa.s), Purified water, Silicified Microcrystalline cellulose, Crospovidone (Type-A), Colloidal Silicon Dioxide, Magnesium stearate and Opadry II white (85F18422). The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 7^{th} Edition in terms of function and quantities.

Manufacture

The finished product manufacturer is Mylan Laboratories Limited located at Plot No. H-12 and H-13), MIDC, Waluj Industrial Area, Aurangabad-431136, Maharashtra, India. The manufacturing site complies with TMDA cGMP standards.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: Description, Identification (HPLC and UV), Dissolution (UV), Uniformity of dosage units (By Mass variation), related substances (HPLC), Assay (HPLC), Water (KF) and microbial tests. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system
Stability studies were conducted on 3 (three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 12 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in blue opaque HDPE Bottle of 60 tablets at or below 30◦C.

Safety and efficacy information

The bio-equivalence study was performed on Darunavir 800 mg film coated tablets and the applicant requests that BE results of the higher strength (Darunavir 800 mg film coated tablets) be extrapolated to the lower strength (Darunavir 600 mg film coated tablets) via bio-waiver. Therefore, safety and efficacy of Durart 600 was established through biowaiver application. Comparative dissolution data was submitted.

The biowaiver was therefore approved based on additional strength.

Durart 600 fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. The following biowaiver criteria are fulfilled: Both the strengths of Darunavir tablets

(600 mg and 800 mg) are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process. The qualitative composition of both the strengths is the same. Both the strengths are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of the active substance is the same for both the strengths

Dissolution profiles of Durart 600 tablets (Darunavir 600 mg) was compared to Durart 800 tablets (Darunavir 800 mg). Similarity factor (f2) values at all media were observed to be above 50, confirming that the dissolution profiles of the two strengths Darunavir tablets (600 mg and 800 mg) are similar. Additionally, the absorption kinetics of Darunavir is linear within the therapeutic dose range of 600 mg – 800 mg.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. Durart 600 is recommended for registration.

5. Post-approval updates

Variation applications: NA

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities: NA

Type of feedback	Impact	Response

Re-registration applications

NA

PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;

Secondary pack label;


75059326
NO VARNISH ZONE
B.No./Lot:
Mfd./Fab.:
Exp.:
Lot: xxxxxxxxx
Mfd.: mmmyyy
Exp.: mmmyyy
* Serial No.: xxxxxxxxxxxxxxxxxxxx
** GTIN No.: xxxxxxxxxxxxxxxxxxxx
GS00 38 01
Darunavir Tablets
DURART 600
600 mg
POM Schedule 2 PP
60 Tablets
Mylan.com
Mylan
Each film coated tablet contains:
Darunavir Ethanolate equivalent to Darunavir 600 mg
Do not store above 30°C.
Store in the original container.
Dosage: As directed by the physician.
NOT TO EXCEED PRESCRIBED DOSAGE.
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.
Indications, Warnings & Precautions: Read the package leaflet before use.
Chaque comprimé pelliculé contient:
Éthanolate de darunavir, équivalant en darunavir à 600 mg
À conserver à une température ne dépassant pas 30°C.
À conserver dans l'emballage d'origine.
Posologie: Comme dirigé par votre médecin.
NE PAS DÉPASSER LA DOSE PRESCRITE.
TENIR HORS DE LA PORTÉE ET DE LA VUE DES ENFANTS.
Indications, Mises en garde et Précautions: Lire la notice avant utilisation.
Darunavir Comprimés
DURART 600
600 mg
POM Schedule 2 PP
60 Comprimés
Mylan.com
Mylan
artwork - 100%
To respect prescribed doses
Respecter les doses prescrites
8 904093 817663
Tanzania Regn No.:
NAFDAC Regn No.:
Zambia Regn No.:
Zimbabwe Regn No.:
Botswana Regn No.:
Namibia Regn No.:
Namibia Scheduling Status: NS2
Mfg. Lic. No./Lic. Fab. No.: AD/089
Mfd. by: / Fab. par:
Mylan Laboratories Limited
H-12 & H-13, MIDC, Waluj,
Aurangabad - 431136, Maharashtra, INDIA
75059326